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Autosomal Dominant and Sporadic Radio-Ulnar Synostosis

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We report on seven cases of congenital radio-ulnar synostosis (RUS). Five were found in the same family and two were sporadic. In six the synostosis was bilateral and consistently involved the proximal end of the radius and ulna. In the familial cases the anomaly was inherited as an autosomal dominant trait and was associated with a Dubois sign and relative shortness of metacarpals number 4 and 5 in two patients, and of number 2 in another patient, and of all phalanges of the 5th fingers. These observations suggest involvement of an ulnar developmental field. RUS does not seem to be rare in the Sicilian population. Am. J. Med. Genet. 68:127–134, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: congenital radio-ulnar synostosis; autosomal dominant; forearm anomaly; Sicily; ulnar developmental field

INTRODUCTION

Congenital radio-ulnar synostosis (RUS) impairs supination and pronation. It is more often bilateral than unilateral and is usually sporadic; familial occurrence is said to be rare [Hansen and Andersen, 1970]. About 300 isolated cases have been reported since the original description in 1793 [Finidori et al., 1978; Griffet et al., 1986].

The Italian Registry on Congenital Malformation (IPIMC) collected one case of RUS within the period 1986–1992, in a total of 766,000 births. In this patient the anomaly was associated with absent left thumb, club hands, right thumb duplication, cervico-vertebral schisis, and anomalous umbilical vessels (Mastroiacovo, personal communication). One isolated case was observed by Camera in Genova [1997]. However, the frequency might be underestimated since the anomaly is not always recognizable at birth.

In Sicily, 18 patients with RUS have been observed. In seven, belonging to two families, RUS was associated with microcephaly [Giuffrè et al., 1994]; four are syndromal cases with Brachmann De Lange syndrome (2), Nager syndrome (1) [Pavone et al., 1988], isotretinoin exposure (1) [Rizzo et al., 1991], and the remainder are the cases reported here.

We describe a family with five affected relatives in three generations. Two unrelated sporadic cases with bilateral and unilateral synostosis, respectively, are also reported. The familial cases represent a complex form of RUS and lend further support to the hypothesized ulnar developmental field.

CLINICAL REPORTS

Patient 1

R.P., a 1-year-old boy, is the first child of healthy, non-consanguineous Sicilian parents (father 28, mother 26 years old). He was delivered at term by caesarean section after a normal pregnancy. Birthweight was 3,250 g. The neonatal period was uneventful. At 4 months, the parents noted that R.P. was unable to pronate or supinate his left arm. At 9 months his weight was 9,000 g (50th centile), length was 68 cm (10th centile), and OFC was 45 cm (50th centile). The boy had an abnormal left arm with deformity of the proximal segment of the radius and ulna. The physical findings were otherwise normal. Roentgenograms showed an abnormal left elbow joint with deformation and fusion of the proximal part of the radius and ulna; the right was normal. Chromosomes were apparently normal.

Patient 2

Z.D., a boy, is the second child of non-consanguineous healthy Sicilian parents (father 35, mother 30 years old). He has an older, healthy brother. The child was born at term with birth weight of 3,850 g, length of 49 cm, and an OFC of 34.5 cm. Infancy and childhood were

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uneventful. At 11 years the patient was evaluated for RUS. At that time he had a weight of 40 kg (75th centile), height of 136 cm (10th centile), and an OFC of 53 cm (50th centile). He had brachycephaly, a wide forehead, frontal bossing, decreased antero-posterior diameter of thorax, and severe limitation of pronation, and supination at the elbow and wrist joints. The boy had borderline intelligence with an I.Q. of 80. There was no taurodontism nor dermatoglyphic abnormalities. Skeletal roentgenograms showed bilateral synostosis of the proximal ends of the radius and ulna. Chromosomes were apparently normal.

Family F

***Patients I-1, II-1* (Fig. 1).** The father of the proposita and her paternal grandfather (36 and 70 years old, respectively) had severe radio-ulnar synostosis which prevented supination and pronation. Both men tended to keep their forearms flexed with the palms facing each other. They were otherwise normal and had normal intelligence. The paternal age of these patients was not advanced when they were conceived. The elbow of patient II-1 is illustrated in Figure 2.

Patient III-1. F.V., a girl, was born normally at term after an uncomplicated pregnancy. Ultrasound examination at 18 weeks of gestation did not show any apparent abnormalities. Her birth weight was 3,500 g, length was 51 cm, and OFC was 35 cm. Her first years of life were uneventful. At 11 years her weight was 37 kg (50th–75th centile), height was 142 cm (50th centile), and OFC was 52 cm (50th centile). Her forehead was narrow and there was a midline facial capillary hemangioma. She kept her forearms flexed (Fig. 3) and pronation and supination were virtually impossible. Her performance in school was reported to be poor and she had severe difficulty in writing, in spite of an I.Q. of 100. Roentgenograms showed bilateral synostosis of the proximal ends of the radius and ulna extending over a length of 4 cm. The carpal bones were normal with no synostosis. A Dubois sign (tip of 5th finger proximal to the DIP joint of the 4th digit) was present and there was relative hypoplasia/shortness of metacarpals 4 and 5 (Fig. 4) and of both 5th fingers. Metacarpophalangeal profile analysis confirmed this impression (Fig. 5). Results of a chromosome analysis and of other laboratory tests were normal.

Patient III-3. F.E., a girl, was born at term after an uneventful gestation. Her birth weight was 3,200 g, length was 50 cm, and OFC was 34 cm. Ultrasound examination at 18 weeks of gestation did not show any abnormalities. The first years of life were uneventful and psychomotor development was normal. At 8 years her weight was 27 kg (75th centile), height was 114 cm (3rd centile), and OFC was 50 cm (50th centile). Pronation and supination were severely limited (Fig. 6). The anomaly appeared identical in both forearms. A grade II/VI systolic murmur could be heard precordially. Her

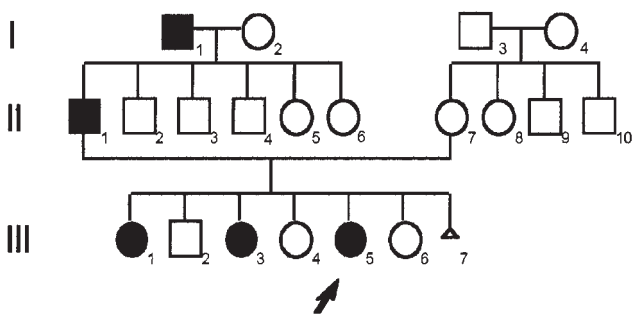

Fig. 1. Pedigree of family F shows occurrence in three successive generations with AD inheritance.

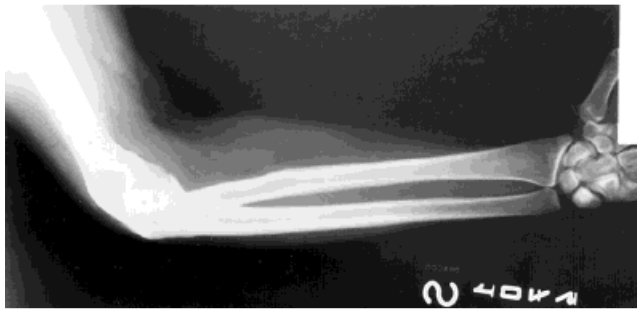

Fig. 2. Patient II-1. Roentgenograms of upper limb. Note proximal radio-ulnar synostosis.

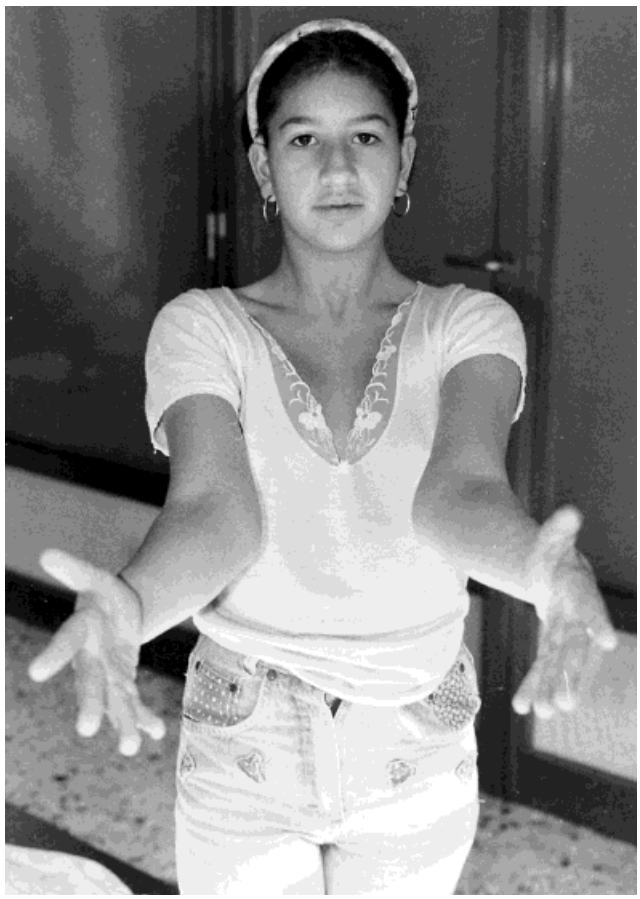

Fig. 3. Patient III-1. Note severe limitation of supination of forearms and hands.

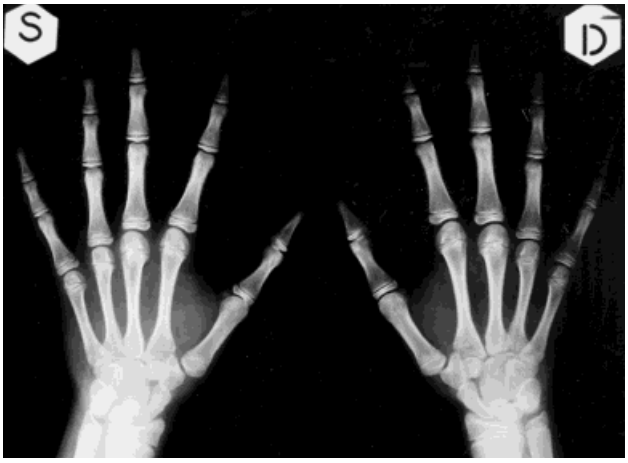

Fig. 4. Patient III-1. Note Dubois sign and relative hypoplasia of 4th and 5th metacarpals.

I.Q. was 110. Roentgenograms demonstrated bilateral radio-ulnar synostosis with proximal fusion that extended distally for about 3 cm (Fig. 7). The carpal bones were normal and without synostosis (Fig. 8). Metacarpophalangeal profile analysis documented shortness of metacarpal 2 and of all phalanges of the 5th fingers (Fig. 9). Chromosomes were apparently normal.

Patient III-5. F.A., the proposita, was born at term after an uneventful gestation. Her birth weight was 3,400 g, length 51 was cm, and OFC was 35 cm. An ultrasound examination at 18 weeks of gestation did not show any apparent skeletal abnormalities. The neonatal period was uneventful and psychomotor development was normal. At 4 years her weight was 16 kg (50th centile), height was 93.5 cm (10th centile), and OFC was 49 cm (25th centile). Supination and pronation were limited. Clinodactyly of the fifth fingers and a right simian crease were also evident. Roentgenograms showed bilateral synostosis between the proximal ends of the radius and ulna; carpal bones were normal with no synostosis. A Dubois sign was present. Shortness of metacarpals 4 and 5 was confirmed by metacarpophalangeal profile analysis (Fig. 10).

DISCUSSION

Congenital radio-ulnar synostosis (RUS) is an anomaly that causes limitation of all movements of the forearm with consequent impairment of hand use. Pronation and supination of the forearm are limited or absent. This anomaly may be associated with other defects such as abnormalities of the olecranon, the clavicles, the ribs, and the sternum [Temtamy and McKusick, 1978], dislocation of the hip, knee, and foot [Mercer, 1950; Freyer, 1966], and syndactyly and polydactyly [Wilkie, 1914; Mercer, 1950; Freyer, 1966]. In patients with RUS a high frequency of associated malformations in other organs such as the heart and urinary tract has been reported [Carroll and Louis, 1974]. RUS is seen in a number of aneuploid syndromes, particularly those involving abnormal numbers of X and Y chromosomes [Cleveland et al., 1969; Schinzel, 1984; De Grouchy and Turleau, 1984]. RUS can be seen in several non-aneuploidy syndromes. The London Dysmorphology Database lists 37 conditions with this anomaly, includ-

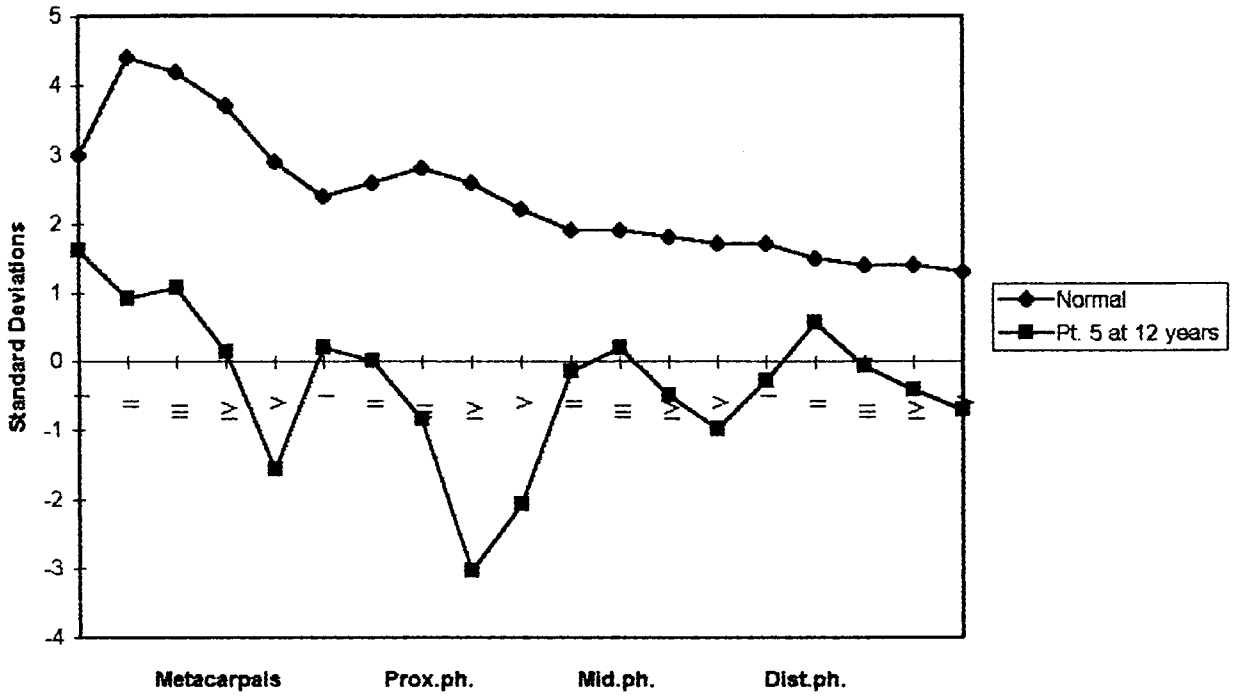

Fig. 5. Patient III-1. Metacarpophalangeal profile analysis documents shortness of metacarpals 4,5.

Fig. 6. Patient III-3. Limited supination of the forearms.

ing recent reports in the Williams-Beuren syndrome [Morris and Carey, 1990; Pankau et al., 1993].

RUS has been divided into two forms: in type 1 there is a proximal, smooth fusion of 2–6 cm between the radius and ulna with absence of the radial head; in type 2 there is a fusion just proximal to the distal radial epiphysis with congenital dislocation of the radial head

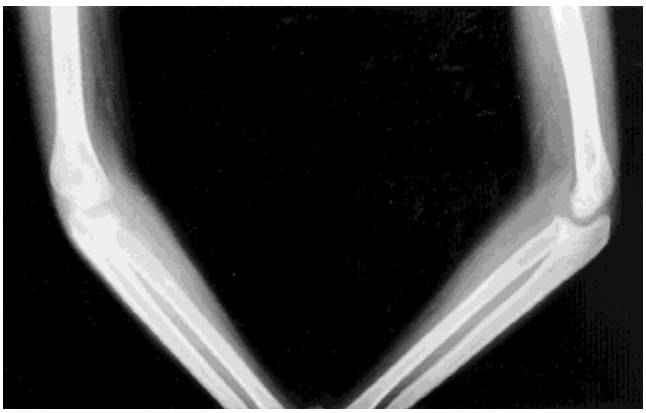

Fig. 7. Patient III-3. Elbow roentgenographs showing radio-ulnar synostosis with proximal fusion.

Fig. 8. Patient III-3. Note shortness of metacarpal 2.

[Mital, 1976; Bauer and Jonsson, 1988]. In type 2 there is also a restriction of extension at the elbow.

Blauth and Von Rothkirch [1989] distinguish 4 degrees of severity of RUS: in the mildest form, there is only "dysplasia" in the proximal radioulnar joint; second-degree malformation is characterized by synostosis exclusively in the proximal radioulnar joint; in third-degree synostoses, the bony bridge extends further distally; and in the rare fourth-degree type there is a complete or almost complete bridge between the two forearm bones.

Table I is a nosologic list of the radio-ulnar synostoses. The non-syndromal forms are divided mainly into two types: A) AD isolated RUS further classified into types I and II, and B) complex RUS.

RUS was present in all of our patients. In case 1 RUS was unilateral (left). Case 2 had bilateral RUS associated with other minor anomalies including decreased antero-posterior diameter of the thorax and borderline intelligence. Clinical signs initially suggested Klinefelter syndrome but this diagnosis was excluded by chromosome analysis. According to the classification of Mital [1976], these two patients belong to isolated RUS, type I. The familial cases represent a complex form of RUS. These patients can be included in the classification of Mital [1976] and Bauer and Jonsson [1988] as type 1 because the radial head is absent. Following the radiological classification of Blauth and Von Rothkirch [1989], our familial cases belong to the third group. These five patients also had a Dubois sign, relative hypoplasia/shortness of the lateral metacarpals, and shortness of phalanges of the 5th fingers, evidence for involvement of the ulnar field [Opitz, 1985; Lewin and Opitz, 1986; Richieri-Costa and Opitz, 1986]. The pedigree shows occurrence in three successive generations with presumed autosomal dominant inheritance and bilateral involvement.

The first report of familial radioulnar synostosis was by Abbott, 1892; approximately 20 families were described subsequently [Davenport et al., 1924; Fahlstrom, 1932; Spritz, 1978; Walter, 1978]. Hansen and Andersen [1970] collected 37 cases of radio-ulnar

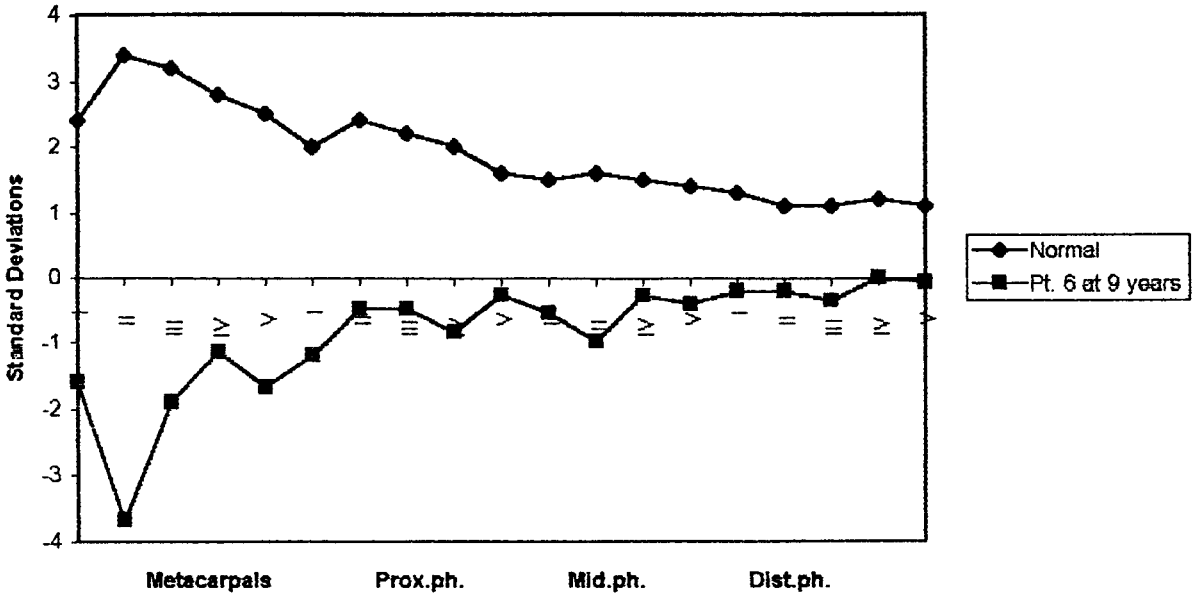

Fig. 9. Patient III-3. Metacarpophalangeal profile analysis documents shortness of metacarpal 2.

synostosis from the clinical files of ten Orthopaedics Departments in Denmark over a 10-year period. Five of these patients had a family history of radio-ulnar synostosis. In one family the defect was present in the proband's father, the paternal grandmother, and three paternal uncles. Spritz [1978] reported bilateral RUS in three generations of a Black American family confirming AD inheritance with incomplete penetrance. According to the data of Walter [1978], AD radioulnar synostosis is bilateral in 39 of 46 patients, whereas sporadic cases are almost equally unilateral and bilateral. However, in one family with AD inheritance over three generations, there were only unilateral cases, two right and two left [Walter, 1978]. If in AD inheritance one side is affected in some cases, and the other side in others, then one would expect that in the occasional het-

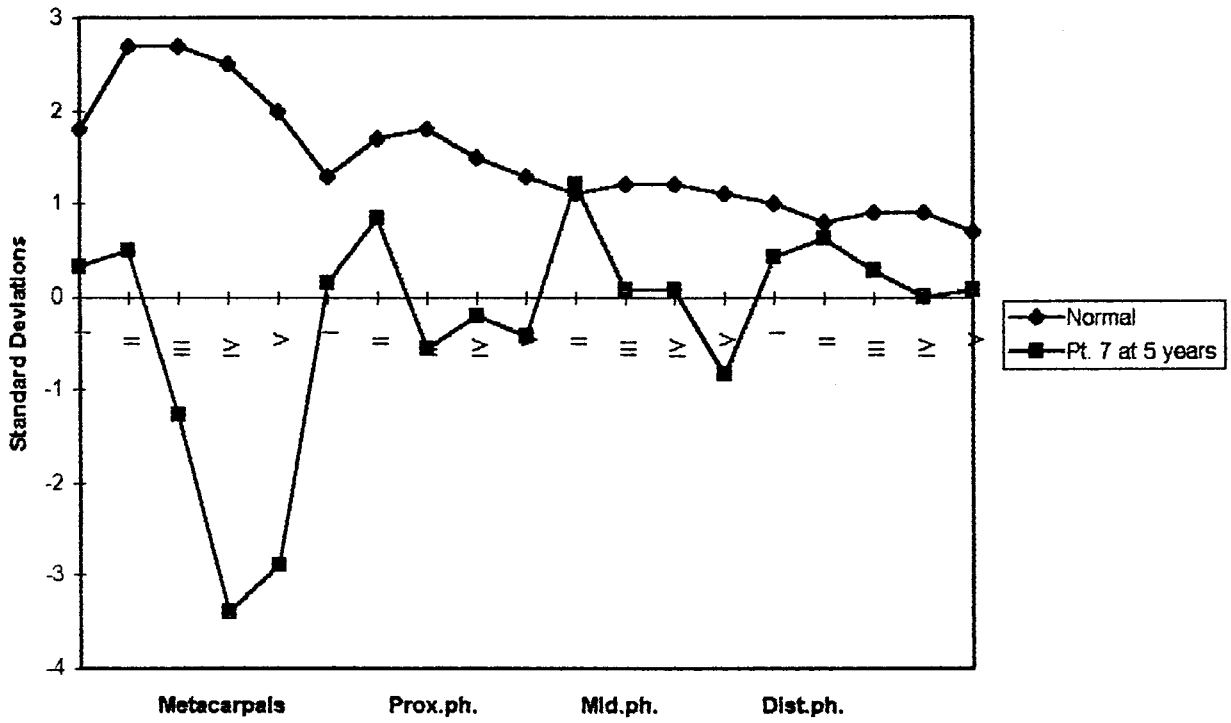

Fig. 10. Patient III-5. Metacarpophalangeal profile analysis documents shortness of metacarpals 4,5.

TABLE I. Radio-Ulnar Synostoses (RUS)

Nonsyndromal forms
A. Isolated RUS-AD, e.g., Davenport et al. [1924]
Types I and II
B. Complex RUS
Type Watterott-Lange with thumb hypo/aplasia-AD [1931]
Catania form with ulnar ray(s) involvement
Syndromal forms-nonaneuploid
Aase syndrome of triphalangeal thumb and congenital anemia [1969]
Abruzzo-Erickson syndrome-X-linked? [1977]
Berant syndrome of radio-ulnar synostosis and craniosynostosis [1973]
Buntinx syndrome of MR, radio-ulnar synostosis, short stature, retinal changes [1991]
Cenani-Lenz syndrome of oligodactyly, synostosis [1967]
Der Kaloustian syndrome of Radio-Ulnar synostosis, macrocephaly, MR, AR [1992]
Femoral hypoplasia, unusual facies [Burn et al., 1984]
Fetal alcohol syndrome [Froster and Baird, 1992]
Fetal thalidomide [Smithells and Newman, 1992]
Fetal vitamin A syndrome [Rizzo et al., 1991]
Gershoni-Baruch syndrome of radial ray defects, omphalocele, diaphragmatic hernia [1990]
Holt-Oram syndrome [Smith et al., 1979; Hurst et al., 1991]
Hutteroth syndrome of absent thumbs, short forearms, heart, short stature, MR [1975]
Jorgenson syndrome of blepharophimosis, radio-ulnar synostosis [1983]
Kelly syndrome of acrofacial dysostosis, short stature, MR [1977]
Lacrimo-auricolo-dento-digital (LADD) syndrome [Wiedmann and Drescher, 1986]
Meinecke-Peper syndrome of frontonasal dysplasia, phocomelia, absent thumbs [1992]
Michels syndrome of clefting, ocular anomalies, radio-ulnar synostosis [1978]
Multiple pterygium syndrome [Hall, 1984]
Nager acrofacial dysostosis [Bowen and Harley, 1974]
Nievergelt syndrome [Petrella et al., 1990]
Pitt syndrome of prenatal growth retardation, MR, unusual facies [1984]
Say syndrome of cloverleaf skull, skeletal dysplasia [1987]
Scapulo-Iliac dysostosis [Kosenow et al., 1970]
Stiles-Dougan syndrome of malformed upper extremities [1940]
Stoll-facioauriculoradial syndrome [Harding et al., 1982]
Tamari-Goodman syndrome of upper limb, cardio-vascular anomalies [1974]
Williams syndrome [Pankau et al., 1993]
Syndromal forms-aneuploid
49,XXXXY
48,XXXX
48,XXXY
48,XXYY
47,XXY
47,XYY
Partial trisomy 11q
trisomy 8 mosaicism
del(13) (q22-qter)
del(10)(pter-p13)
dup(12)(q24-qter)
dup(14)(q23-qter)
tri(18p)

erozygotes neither side is affected; however, such cases of failure of penetrance are only rare [Abbott, 1892]. Abruzzo and Erickson [1977] observed right RUS in an uncle and his nephew. They and a brother of the nephew had hypospadias, hearing loss, and shortness of stature. In addition, the two brothers had cleft palate, an iris coloboma, and the uncle had a bifid uvula. This could represent an X-linked recessive disorder. X-linkage may be responsible for the fact that among 127 published cases, 61% were male and 39% female [Walter, 1978].

Recently, Giuffrè et al. [1994] described two Sicilian families in which seven members each had radio-ulnar synostosis and microcephaly. The pattern of inheritance was autosomal dominant with an apparent excess of affected females. The radio-ulnar synostosis was similar to that seen in the present patients. The microcephaly was accompanied by mild psychomotor delay in the males, while females were of normal intelligence.

In the IPIMC registry RUS is rare (1:766,000 births); however, in the Sicilian population of 60,000 births 18 cases were studied recently, the familial ones clearly falling into two different types. None of our patients had an aneuploid syndrome. Considering undetected mild forms it seems reasonable to view 18/60,000 a gross underascertainment.

On the basis of the experience reported by Kelikian and Doumanian [1957] and Hansen and Andersen

[1970], it is not considered advisable to treat this anomaly surgically; unsatisfactory results are due to underdevelopment of the associated muscles and other soft tissue. However, based on their experience with 29 RUS cases, Griffet et al. [1986] suggested there is postoperative improvement in the use of forearms and hands. These authors suggest surgery only for children between the ages of 4 and 10 years with severe functional disabilities.

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